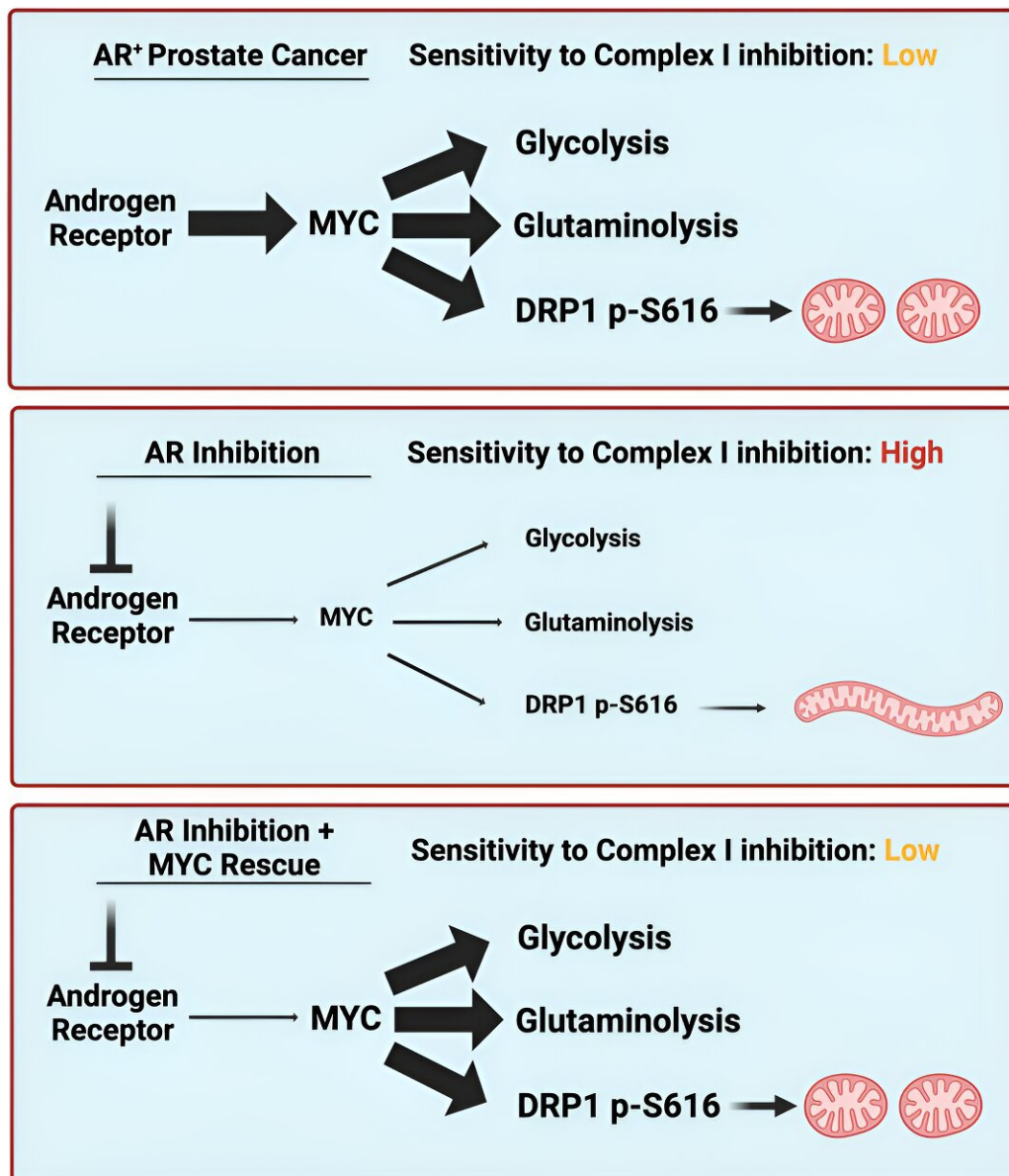


Studies help explain why some prostate cancers become resistant to hormone therapy

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Graphical abstract. Credit: *Cell Reports* (2023). DOI: 10.1016/j.celrep.2023.113221

Two new studies led by researchers from the UCLA Jonsson Comprehensive Cancer Center give insight into how cells use energy to influence the way prostate tumors survive and grow—advancements that can help explain why some prostate cancers become resistant to hormone therapy, the most commonly used treatment for men with advanced stages of the disease.

Hormone therapy, also known as anti-androgen therapy, plays a crucial role in temporarily halting the growth of prostate cancer cells. Over time, however, the majority of patients eventually see their cancer return and progress, underscoring the pressing need for continued advancements to enhance clinical outcomes.

"Identifying metabolic alterations and understanding patterns in cancer cells could be a critical component to developing new cancer treatments," said Andrew Goldstein, associate professor of molecular, cell and developmental biology and urology at the David Geffen School of Medicine at UCLA and member of the UCLA Jonsson Comprehensive Cancer Center.

"New technological advances are giving us insight into actually how these tumors are breaking down their nutrients—known as [cancer metabolism](#)—to help them grow. And we might be able to harness or exploit that biology to make tumors more treatable."

Metabolic insights reveal treatment sensitivity and resistance pathways

In the [first study](#), published in *Nature Cell Biology*, a team of investigators identified a specific process in prostate cells that helps determine how they evolve from one type of cell to another, which plays a crucial role in determining a response to treatment.

There are two types of cells in the prostate: basal and luminal cells. Whether cancer initially starts in a basal cell or a luminal cell, it almost always takes on the properties of luminal cells as the cancer grows. But over time, and in response to treatment, some tumors become less luminal.

When a tumor is very luminal, it is more treatable using hormone therapy. And when it's less luminal, it's less treatable and more resistant, noted Goldstein, who is the senior author of the study and a member of the Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research at UCLA.

While studying this process, researchers saw that when basal cells transform into luminal cells, the way they process a molecule called pyruvate changes. These changes in metabolism can influence the "genetic instructions" within the cells that determine how they develop and respond to treatment.

The team discovered that blocking a specific part of cell metabolism, called the mitochondrial pyruvate carrier, and adding a substance called lactate can change the cell behavior. These changes could potentially affect the success of treatments for prostate cancer, especially those targeting the androgen receptor, a key player in prostate cancer growth.

Additionally, altering how cells use a substance called lactate can cause significant changes in how the DNA is organized in the cells, affecting which genes are turned on or off.

"The study highlights the importance of considering how altering cell metabolism could impact prostate cancer and its response to treatment," said first author of the study Jenna Giafaglione, a graduate student in UCLA's Molecular Biology Interdepartmental Program and member of the Goldstein lab as well as the lab of Paul Boutros, director of cancer data science at the UCLA Jonsson Comprehensive Cancer Center.

"If we know that certain aspects of metabolism are promoting a resistant phenotype, then we can go after new targets in those resistant tumors."

MYC protein identified as key regulator

The second study, published in the journal [Cell Reports](#), sheds new light into how prostate cancer cells react when the [androgen receptor](#) pathway is blocked, which is a common approach in treating advanced prostate cancer.

To understand what happens to the cell's energy production and usage in response to this blocking, Goldstein and his team looked at how the cancer cells change the way they produce energy. They found that cells start out depending on a type of energy inside the mitochondria, pinpointing certain molecules and processes within the cell that control these changes.

One important protein in this process, called MYC, was found to be the critical regulator of the behavior. Specifically, they saw that if MYC activity decreases as a consequence of the therapy, then these cells seem to become very reliant on their mitochondria to survive. If MYC does not go down, then the cells are much more resilient and resistant to therapy, and not reliant on their mitochondria. Boosting MYC activity reversed the changes in energy production, making the [cancer cells](#) less sensitive to certain inhibitors.

"This study teaches us about treatment response and also suggests that if we could find the right combination of therapies, for example, to use [hormone therapy](#) initially, and then to use some kind of secondary therapy that influences the mitochondrial behavior, we might be able to reduce disease progression and recurrence," Goldstein said.

Taken together, the new studies demonstrate a need to further study the link between metabolism and treatment resistance or treatment response. Understanding and controlling these changes could potentially help develop better treatments for [prostate](#) cancer.

More information: Prostate lineage-specific metabolism governs luminal differentiation and response to antiandrogen treatment, *Nature Cell Biology* (2023). [DOI: 10.1038/s41556-023-01274-x](https://doi.org/10.1038/s41556-023-01274-x) , www.nature.com/articles/s41556-023-01274-x

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